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Genetics of Focal Epilepsies: What Do We Know and Where Are We Heading?

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This article is based on a lecture delivered at the 2017 American Epilepsy Society Annual Meeting and provides an overview of the growing evidence supporting the strong genetic contribution to focal epilepsies. This also discusses how advances in the molecular genetics of focal epilepsies are rapidly translating to routine clinical care.

Introduction

Focal epilepsies account for 60% of all forms of epilepsy (1) and traditionally have been regarded as largely acquired disorders. This perception is related to the common observation that the epilepsy resulting from an environmental insult—such as a stroke, head trauma or tumor—is focal (2). Growing evidence, however, indicates that genetic factors play a major role in the pathogenesis of focal epilepsies (3). This article provides an overview of this evidence and discusses how advances in this area are rapidly translating to routine clinical practice.

Genetic Contributions to Focal Epilepsies: What Is the Evidence?

Familial Aggregation Studies

Familial aggregation studies estimate the magnitude of risk of a certain disease among relatives of affected probands (4). Early studies suggested an increased risk of seizure disorders among relatives of probands with focal epilepsy (1.7–4.4%) compared to the general population (0.5–1%; 2). However, these investigations had several methodological limitations, including possible selection bias, small sample size, lack of controls, reliance on patient interviews to ascertain family history, failure to adjust for age in relatives, and ambiguous definitions of epilepsy (5).

The low number of population-based studies indicate that the risk of epilepsy or unprovoked seizures among first-degree relatives of individuals with focal epilepsy is two- to threefold greater than in the general population (5–9). The risk varies depending on the etiology of the proband's epilepsy. A U.S. population-based study found that when compared with the general population, the risk of epilepsy was more than twice as high in first-degree relatives of probands with focal epilepsy of unknown cause (standardized incidence ratio [SIR]: 2.2, 95% CI: 1.07–3.48; 5). A similar risk estimate was seen in relatives of probands with idiopathic focal epilepsy (SIR: 2.7, 95% CI: 0.00–6.81) but did not reach statistical significance due to small numbers. Among relatives of probands with focal epilepsy of structural/metabolic cause, the risk was increased by almost fivefold when the proband's epilepsy had prenatal/developmental causes (SIR: 4.8, 95% CI: 1.56–9.88) but was not increased significantly when the proband's epilepsy was due to postnatal causes (SIR: 1.3, 95% CI: 0.26–2.53).

Twin Studies

Under certain assumptions, a higher concordance for a disease in monozygotic twins than in dizygotic twins suggests a genetic contribution to the disease (10). Furthermore, the magnitude of concordance in monozygotic twins, coupled with the extent to which this exceeds that in dizygotic twins, are indicators of the size of the genetic contribution (10).

Twin studies report higher concordances for focal epilepsy in monozygotic twins (0.21–0.40) than in dizygotic twins (0.03–0.12; 11–14). Concordances vary depending on the underlying etiology and the syndrome (12–14). In an Australian study of 418 twin pairs with seizures (14), concordance was higher in monozygotic twins than in dizygotic twins for nonlesional temporal lobe epilepsy (0.82 vs 0, $p = 0.003$). Notably, concordances did not differ between monozygotic and dizygotic twins for idiopathic focal epilepsies (0 vs 0.17, $p = 0.3$), comprising childhood epilepsy with centrotemporal spikes and benign occipital epilepsies, which have long been considered to be largely genetic in origin. No differences were found between monozygotic and dizygotic twins for symptomatic focal epilepsies (0.08 vs 0, $p = 0.2$).

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Clinical Descriptions of Familial Focal Epilepsy Syndromes

Several familial focal epilepsies have been identified, mostly displaying Mendelian inheritance. Not only have these syndromes provided further evidence for genetic contributions in focal epilepsies but have also led to important gene discoveries (Table 1). The clinical characteristics of four main syndromes are summarized as follows, and their molecular underpinnings are discussed in the next section.

Autosomal Dominant Sleep-Related Hypermotor Epilepsy (ADSHE)

ADSHE (previously known as "autosomal dominant nocturnal frontal lobe epilepsy") is characterized by seizures beginning in the first 2 decades of life (15, 16). The predominant pattern is clusters of brief nocturnal focal motor seizures, with hyperkinetic or tonic manifestations, occurring shortly after falling asleep or before awakening. Many affected individuals experience an aura and retain awareness during the events. Seizures can be misdiagnosed as normal sleep behavior, parasomnias, or psychiatric disorders. About two-thirds of cases have also focal to bilateral tonic–clonic seizures. There is marked intrafamilial variation in severity. Most patients are of normal intellect, have unremarkable EEG and neuroimaging, and respond to carbamazepine. However, a severe form of ADSHE has been described with drug-resistant epilepsy, psychiatric comorbidities, and intellectual disability (17). ADSHE displays autosomal dominant inheritance, with a penetrance of ~70% (15).

Familial Mesial Temporal Lobe Epilepsy (FMTLE)

FMTLE is a typically benign syndrome (18, 19) that accounts for one-fifth of new diagnoses of nonlesional mesial temporal lobe epilepsy (20). Onset is usually in adolescence or early adulthood, with no antecedent febrile seizures. The predominant or sole seizure type is focal aware seizure with intense déjà vu and, less commonly, epigastric discomfort, perceptual distortions, and fear. Symptoms are often perceived as "normal" experiences by affected individuals and may not be detected by clinicians without specific inquiries, which explains why the syndrome is underdiagnosed. When present, focal impaired awareness seizures are infrequent and focal to bilateral tonic–clonic seizures rare. EEG is generally uninformative, and neuroimaging is normal. Seizures are easily controlled with antiepileptic drugs and may even remit spontaneously. However, a clinically heterogeneous form of FMTLE often associated with antecedent febrile seizures, hippocampal sclerosis, and drug resistance has also been described (21). FMTLE exhibits complex inheritance (19), but rare dominant families have also been reported (22).

Autosomal Dominant Epilepsy With Auditory Features (ADEAF)

ADEAF typically begins in adolescence or early adulthood, with no antecedent risk factors (23, 24). Hallmarks are focal aware seizures with prominent auditory symptoms or receptive aphasia. Auditory symptoms mainly include elementary hallucinations (e.g., humming, buzzing, or ringing) and, less commonly, illusions or complex hallucinations. Focal impaired awareness seizures and focal to bilateral tonic–clonic seizures may also occur. Neurological examination is normal. Two-thirds of cases show interictal EEG epileptiform discharges, mainly in the temporal region. Neuroimaging is normal. Seizures usually respond to antiepileptic drugs. Inheritance is autosomal dominant, with an estimated prevalence of 67% (25).

TABLE 1. *Familial Focal Epilepsy Syndromes and Genes Implicated in Their Pathogenesis*

Familial Focal Epilepsy Syndrome	Genes
Autosomal dominant sleep-related hypermotor epilepsy (ADSHE)	*CHRNA4*, *CHRNA2*, *CHRNB2*, *DEPDC5*, *KCNT1*, *NPRL2*, *NPRL3*
Autosomal dominant epilepsy with auditory features (ADEAF)	*LGI1*, *RELN*
Autosomal dominant rolandic epilepsy with speech dyspraxia	*GRIN2A*
Benign familial neonatal epilepsy	*KCNQ2*, *KCNQ3*
Benign familial neonatal-infantile epilepsy	*KCNQ2*, *SCN2A*
Benign familial infantile epilepsy	*KCNQ2*, *KCNQ3*, *PRRT2,* SCN2A, SCN8A*
Familial focal epilepsy with variable foci (FFEVF)	*DEPDC5, NPRL2*, *NPRL3*
Familial mesial temporal lobe epilepsy (FMTLE)	*DEPDC5*
Familial posterior quadrant epilepsies	Unknown
Partial epilepsy with pericentral spikes	Unknown

*Main gene for benign familial infantile epilepsy.

Familial Focal Epilepsy With Variable Foci (FFEVF)

The striking feature of FFEVF is marked intrafamilial variability in seizure semiology and EEG abnormalities, with seizures arising from different brain regions (i.e., frontal, temporal, parietal, or occipital) in different family members (26, 27). However, focal seizure semiology and congruent EEG abnormalities remain constant within individuals. Age of seizure onset is also variable, ranging from infancy to adulthood. Individuals typically have normal intellect with no abnormalities on neurological examination. Neuroimaging is normal. Response to antiepileptic drugs is variable, but in most cases seizures can be easily controlled. Inheritance is autosomal dominant, with penetrance of ~60% (26).

Gene Discoveries

Remarkably, the first epilepsy gene to be discovered was for focal epilepsy: *CHRNA4*, encoding the nicotinic acetylcholine

receptor α4 subunit, identified in 1995 in a large pedigree with ADSHE (28). This heralded a pioneering era of epilepsy gene discoveries, including several focal epilepsy genes, such as the voltage-gated potassium channel genes *KCNQ2* and *KCNQ3*, associated with benign familial neonatal epilepsy (29–31); the voltage-gated sodium channel α2 subunit gene *SCN2A*, linked with benign familial neonatal–infantile epilepsy (32); and *LGI1*, encoding a neuronal secreted protein, associated with ADEAF (33).

The advent of next-generation sequencing (NGS) in the mid-2000s accelerated the discovery of focal epilepsy genes (3). A major breakthrough was discovering that genes encoding components of the GATOR1 complex (*DEPDC5*, *NPRL2*, *NPRL3*)—a negative modulator of the mammalian target of rapamycin (mTOR) pathway—have an important role in focal epilepsies (22). Germline mutations in *DEPDC5* were initially identified in 7/8 large pedigrees with FFEVF and in 10/82 (12%) smaller families with nonlesional focal epilepsy (34). *DEPDC5* mutations were subsequently detected in other, mostly familial, focal epilepsies, including ADSHE, FMTLE, and ADEAF, and even in focal epilepsies with brain malformations (22). Germline mutations in *NPRL2* and *NPRL3* were reported in a few families and individuals with focal epilepsy, with or without brain malformations (35).

These findings expanded the spectrum of neurological disorders associated with dysregulation of the mTOR pathway—the "mTORopathies"—the archetype of which is tuberous sclerosis. Brain somatic mutations in mTOR pathway genes are also involved in various malformations of cortical development often associated with focal epilepsy, such as focal cortical dysplasia and hemimegalencephaly (36).

NGS brought other important focal epilepsy gene discoveries: *PRRT2*, encoding a protein expressed in the central nervous system that is thought to be involved in synaptic transmission release, has been associated with an expanding spectrum of paroxysmal disorders, including benign infantile epilepsy, infantile convulsions and paroxysmal choreoathetosis, and paroxysmal kinesigenic dyskinesia (37). *KCNT1*, encoding a sodium-gated potassium channel subunit, has been linked with severe early-onset epilepsies, including epilepsy in infancy with migrating focal seizures and severe ADSHE (38, 39). *GRIN2A*, encoding the N-methyl-D-aspartate receptor NR2A subunit, has been implicated in the epilepsy-aphasia spectrum, comprising typical and atypical childhood epilepsy with centrotemporal spikes, Landau–Kleffner syndrome, and epileptic encephalopathy with continuous spike-and-wave in slow-wave sleep (40).

The role of established epilepsy genes has also been reappraised. A genome-wide association study has suggested that variation in the sodium channel α1 subunit gene *SCN1A*, a well-recognized cause of genetic epilepsy with febrile seizures plus (GEFS+) and Dravet syndrome, may raise the risk for mesial temporal lobe epilepsy with hippocampal sclerosis and febrile seizures (41).

Although most of the identified molecular defects pertain to rare syndromes, recent data indicate that they can also contribute to common focal epilepsies. In a whole-exome sequencing (WES) study (42), the frequency of ultra-rare deleterious variants in known dominant epilepsy genes was higher among 525 individuals with nonlesional focal epilepsy and a family history of epilepsy in at least a third-degree relative ("familial nonacquired focal epilepsy") compared to 3,877 unaffected controls (odds ratio: 3.6, 95% CI: 2.7–4.9, $p = 1.1\times10^{-17}$). No significant differences were found between individuals with nonlesional focal epilepsy and no known family history of epilepsy ($n = 662$) and the same controls. For the group with familial nonacquired focal epilepsy, five established epilepsy genes (*DEPDC5*, *LGI1*, *PCDH19*, *SCN1A*, and *GRIN2A*) ranked as the top genes enriched for ultra-rare deleterious variation, contributing to the risk of epilepsy in ~8% of the individuals.

Incorporating Genetic Testing in the Routine Care of Focal Epilepsies

Driven by decreasing costs, NGS is increasingly utilized in routine clinical practice. Four studies have evaluated its diagnostic yield in focal epilepsy (Table 2). Three studies in patients with different epilepsies referred for genetic testing showed that the diagnostic yield of NGS (gene panels or WES) in those with focal epilepsy was 16% to 29% (43–45). The fourth study applied WES with targeted gene analysis in 40 patients with MRI-negative focal epilepsy and a family history of febrile seizures or any type of epilepsy in at least one first- or second-degree relative (46). Notably, most patients (80%) had only a single affected relative, where expectations of finding a mutation are lower compared to large multiplex families. Targeted WES identified a pathogenic or likely pathogenic variant in 12.5% of cases. Patients with an identified mutation were younger at seizure onset (typically in childhood) compared to those without, as often observed in genetic epilepsies. In a patient with drug-resistant temporal lobe epilepsy, identifying a pathogenic variant in *SCN1A* prompted to halt presurgical investigations due to concern of unfavorable postsurgical outcome (47); it also led to discontinuing longstanding carbamazepine therapy (a potentially aggravating agent in *SCN1A* epilepsies), resulting in seizure freedom.

Aside from *SCN1A* mutations, other molecular diagnoses can influence clinical management in focal epilepsies (Table 3). The treatment of *KCNT1* epilepsies with quinidine has received much attention, as this agent reverses the increased potassium channel function caused by *KCNT1* mutations (48). However, in a recent randomized trial, quinidine was ineffective in severe ADSHE caused by *KCNT1* mutations (49), possibly due to dose-limiting cardiac toxicity occurring at low doses.

Conclusion

There is a strong genetic contribution to focal epilepsies. Considerable progress has been made in elucidating their molecular underpinnings, but for most cases, the genetic defect remains elusive. How do we bridge this gap? Deep phenotyping remains important to identify new syndromes, which in turn can guide novel gene discoveries. The role of somatic mutations should continue to be investigated, as they may underlie nonlesional focal epilepsies (50) in addition to brain malformations. Increasing use of whole genome sequencing can clarify the relevance of non-coding variation in focal syndromes. We await major advances from large collaborations

TABLE 2. ***Studies Investigating the Diagnostic Yield of Clinical Genetic Testing in Focal Epilepsy***

Study	Study Design	Type of Genetic Testing	Patients	Details on Patients With Focal Epilepsy	Diagnostic Yield in Patients With Focal Epilepsy
Moller et al. (43)	Retrospective study of consecutive DNA samples from Denmark, Estonia, the UK, Argentina, and Pakistan	Gene panel (46 epilepsy genes)	216 patients with different forms of epilepsy. <10% of all patients had previous testing for selected genes. *44/216 patients had focal or multi-focal epilepsies*.	Subgroup with focal or multifocal epilepsy included "benign familial neonatal seizures, benign familial infantile seizures, and autosomal dominant nocturnal frontal lobe epilepsy"	7/44 patients (16%)
Helbig et al. (44)	Retrospective study of consecutive DNA samples sent to Ambry Genetics Laboratory	WES with varying gene analysis strategies (limited to known disease genes, or comprising both known and novel disease genes)	1,131 patients with different disorders, including 314 patients with seizures.* 30% of patients with seizures had previous gene panel testing, and 80% had single-nucleotide polymorphism array or array-comparative genomic hybridization. *41/314 patients with seizures had focal epilepsy*.†	Subgroup with focal epilepsy comprised: benign rolandic/ rolandic epilepsy (n = 2); frontal lobe epilepsy (n = 3); temporal lobe epilepsy (n = 8); occipital lobe epilepsy (n = 2); unclassified focal epilepsy (n = 26).	12/41 patients (29%)
Perucca et al. (46)	Prospective study of consecutive patients recruited from the epilepsy outpatient clinics or inpatient video-EEG monitoring units at the Royal Children's Hospital and Royal Melbourne Hospital, Australia	WES with targeted gene analysis (64 epilepsy genes)	40 patients (aged >4 weeks) with MRI-negative focal epilepsy and a family history of febrile seizures or any type of epilepsy in at least one first- or second-degree relative. Exclusion criteria were previous genetic testing (except for chromosomal microarray), severe intellectual disability, and benign focal epilepsies of childhood.	There were 24 males and 16 females; 12 children and 28 adults. Median age at seizure onset (range): 17.5 years (8 months–70 years). The group comprised: temporal lobe epilepsy (n = 24); frontal lobe epilepsy (n = 6); parietal lobe epilepsy (n = 1); occipital lobe epilepsy (n = 1); undefined focal epilepsy (n = 8). Thirty-two patients had one affected first- or second-degree relative, 5 had two, and 3 had three or more. One patient had mild intellectual disability.	5/40 patients (12.5%)
Oates et al. (45)	Prospective study of patients referred to the King's Health Partners epilepsy genetics service, UK	Gene panels (45–102 epilepsy genes)‡	96 patients with early-onset (<2 years) epilepsy, treatment-resistant epilepsy of unknown cause, or familial epilepsy where the genetic cause was unknown. 77% of all patients had previous array comparative genomic hybridisation. *28/96 patients had focal epilepsy*.§	The subgroup with focal epilepsy comprised: benign neonatal epilepsy (n = 2); febrile seizure/ temporal lobe epilepsy spectrum (n = 4); nocturnal frontal lobe epilepsy/sleep-hypermotor epilepsy (n = 6); familial focal epilepsy (n = 8); refractory focal epilepsy (n = 8).	5/28 patients (18%)

Abbreviation: WES, whole exome sequencing.
*123/314 patients with seizures could not be classified due to lacking or incomplete clinical data.
†One patient with benign familial neonatal seizures (unknown WES results) was not grouped with patients with focal epilepsy.
‡Two patients were referred to the epilepsy genetics service with existing positive gene panel results.
§This subgroup does not include any of the 11 patients with "epilepsy-aphasia spectrum," some of whom might have had focal epilepsy (i.e., typical or atypical childhood epilepsy with centrotemporal spikes), but no details were available.

TABLE 3. ***Examples of Management Implications of Detecting Mutations in Genes Associated With Focal Epilepsy***

Genes Associated With Focal Epilepsy	Management Implications
SCN1A	Avoid sodium-channel blocking antiepileptic drugs due to the risk of seizure aggravation; if surgery is considered, counsel patients about the potential risk of postoperative seizure recurrence
SLC2A1	Ketogenic diet as first-line therapy
TSC1, *TSC2*	Consider mTOR inhibitors (e.g., everolimus)
POLG	Avoid valproic acid due to risk of hepatic failure
GRIN2A	Consider memantine?
DEPDC5, *NPRL2*, *NPRL3*	Consider mTOR inhibitors?

that can unravel the genetic contribution to common epilepsies. As molecular discoveries increase, so do opportunities for targeted approaches in focal epilepsies, for which the era of precision medicine has just begun.

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